

REVIEW SERIES

Lung cancer • 4: Chemotherapy for non-small cell lung cancer: the end of the beginning

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The development of chemotherapy for NSCLC over the last 20 years is reviewed, particularly with regard to its palliative effects. New "fourth generation" agents designed to inhibit specific biological pathways thought to be crucial to tumour growth give cause for optimism in the future treatment of NSCLC.

*"Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning"**

BACKGROUND

In 1948 the journal *Cancer* carried a paper titled "The use of nitrogen mustards in the palliative treatment of carcinoma (with particular reference to bronchogenic carcinoma)".¹ This was the first reference to chemotherapy in lung cancer and the principal author was David Karnofsky. Indeed, it was in this paper that the numerical scale describing performance status developed by Karnofsky was first reported. Some of the cases in this original paper gaining palliative benefit had non-small cell lung cancer (NSCLC). From this auspicious beginning there then followed a gap of almost 40 years in which there was little progress, at least in NSCLC. One problem was that the so-called "first generation" agents—including methotrexate, cyclophosphamide, vincristine, and doxorubicin—were essentially inactive in NSCLC, despite being widely used in the 1970s and 1980s in SCLC. In the late 1980s experience with the "second generation" drugs—cisplatin, ifosfamide, mitomycin, vindesine, vinblastine, and etoposide—increased. For the first time worthwhile objective responses were observed. Several combinations of agents were tested with cisplatin apparently the key to this early success.

This review will chart the development of chemotherapy in NSCLC during the last 20 years, discussing its role in advanced disease, as a neoadjuvant therapy before definitive surgery, as an adjuvant after surgery, in subgroups of patients defined by age and performance status, and in patients who relapse after a response to primary chemotherapy. The use of chemotherapy for palliation will be explored. The extensive evaluation of "third generation" agents (paclitaxel, docetaxel, gemcitabine and vinorelbine) in

the 1990s will be summarised, as will early results from the new "biological" or "fourth generation" agents (such as Iressa) in which so much optimism is invested. Finally, an estimate of the potential demand for chemotherapy in NSCLC in England and Wales will be presented.

META-ANALYSES

Despite approximately 50 randomised trials over the past 30 years examining the efficacy of chemotherapy in NSCLC, its role remained uncertain primarily because these trials were too small to detect modest treatment effects reliably.

In 1995 a meta-analysis using updated individual patient data on 9387 randomised cases from 52 available trials (published and unpublished) was therefore conducted by the Non-Small Cell Lung Cancer Collaborative Group in an attempt to evaluate the effects of cytotoxic treatment on survival.² This group investigated the effect of chemotherapy (CT) in four main treatment settings: early disease (surgery *v* surgery+CT; surgery+radiotherapy (RT) *v* surgery+RT+CT), locally advanced disease (radical RT *v* radical RT+CT), and advanced disease (supportive care (SC) *v* SC+CT). The results for cisplatin containing regimens favoured chemotherapy in all groups and attained statistical significance when combined with radical RT and SC. The absolute survival benefit for radical RT+CT was 4% at 2 years. The absolute benefit at 1 year for SC+CT was 10%.

This meta-analysis provided the most reliable estimate of the average effect of chemotherapy in NSCLC of varying stages and suggested that cisplatin based regimens have a valid role in the treatment of this disease. However, no determination of other essential drugs for improved survival could be made due to the heterogeneity of these trials. Large randomised trials are required to overcome the problems of meta-analysis and provide information on the choice of regimens, associated toxicity, and quality of life outcomes.

CHEMOTHERAPY IN REGIONALLY ADVANCED UNRESECTABLE NSCLC

There have been three substantial trials including more than 350 cases addressing the use of chemotherapy in regionally advanced unresectable NSCLC. In a UK trial which compared up to four cycles of mitomycin, ifosfamide and cisplatin (MIC) followed by radiation therapy with radiation therapy alone in 446 patients, no statistically significant survival advantage was found with the addition of MIC, although there was a trend in favour of chemotherapy.³ The result was almost identical to that reported by Le Chevalier *et al*⁴ in

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*Winston Churchill, Speech at the Lord Mayor's Day
Luncheon, London, 10 November 1942.

a French trial of similar design involving 353 patients. Survival at 1 year was 41% for RT alone in both trials compared with 50% and 49% in the CT+RT arms in the French and UK trials, respectively. At 2 years the corresponding figures for RT alone were 14% (French trial) and 16% (UK) compared with 21% and 20%, respectively, for CT+RT in the two trials. A later analysis of the French trial reported a statistically significant benefit for CT+RT compared with RT alone.⁵ Final results from an intergroup trial in the USA which included only “good risk” patients also showed a significant benefit in 458 eligible patients, with very similar incremental improvements in survival to those in the European trials from the addition of cisplatin plus vinblastine for just 2 months.⁶

CHEMOTHERAPY IN ADVANCED UNRESECTABLE NSCLC

The many small trials comparing cisplatin based chemotherapy with standard palliative care (sometimes inappropriately called “best supportive care”⁷) have been adequately summarised with the meta-analyses, and a significant survival advantage is clearly achieved. There is no place for further trials with this randomisation in patients with ambulatory performance status. Five questions, at least, remain:

- Are the conclusions from the small trial meta-analysis confirmed by big trials?
- Do other end points such as quality of life influence the treatment decision?
- Are there subsets of patients gaining more or less from the intervention?
- What about elderly patients?
- What proportion of patients with NSCLC should be considered for chemotherapy?

Are the conclusions from the small trial meta-analysis confirmed by big trials?

Only two trials with over 200 randomised cases address this question, and one of these is a three arm trial. Thongprasert *et al*⁸ randomly allocated 287 patients with WHO performance status (PS) 0, 1 or 2 with stage IIIB or IV NSCLC to receive chemotherapy with ifosfamide, epirubicin and cisplatin (IEP), mitomycin, vinblastine and cisplatin (MVP), or “best supportive care” (BSC). Patients who received chemotherapy lived significantly longer. Cullen *et al*⁹ included 351 patients aged 75 or less with WHO PS 0, 1 or 2 who were randomly allocated to receive MIC or palliative care (PC) alone. The median and 1 year survival rates were 4.8 months and 17% in the PC arm compared with 6.7 months and 25% in the MIC arm ($p=0.03$).

Do other end points such as quality of life influence the treatment decision?

Palliative chemotherapy—defined as treatment in circumstances where the impact of intervention is insufficient to result in major survival advantage but improves tumour related symptoms⁹—is not a new concept. As mentioned above, the very first study of chemotherapy in lung cancer in 1948 reported symptom relief including some patients with NSCLC.¹ Research efforts since then have focused on the aim of extending life, and concerns about side effects have diverted attention away from the palliative potential of chemotherapy. Recent progress in chemotherapy (such as new drug and analogue development) and in supportive care (such as effective anti-emetics) has substantially reduced the toxicity of chemotherapy and required recalculation of the risk/benefit equation. Furthermore, patients may be more prepared to accept some toxicity for effective palliation than for modest extension of life. In a recent American study 81 patients with advanced NSCLC who had been previously treated with cisplatin based chemotherapy were asked to indicate the minimal survival benefit required to accept the toxic effects of chemotherapy.¹⁰

Interestingly, 68% chose chemotherapy for a significant reduction in symptoms even if there was no prolongation of life, but only 22% would accept chemotherapy over supportive care for a survival benefit of 3 months. The median survival threshold for accepting chemotherapy was 4.5 months for mild toxicity and 9 months for severe toxicity.

So how effective is chemotherapy in the palliation of advanced NSCLC, and does any improvement in tumour related symptoms outweigh the negative effects of chemotherapy on quality of life?

Mitomycin, ifosfamide, cisplatin (MIC)

When we launched our randomised trials of MIC chemotherapy versus standard therapy in the late 1980s our prejudice was that, if there was a survival advantage, it would be small and possibly outweighed by the side effects of treatment. To measure this we incorporated a cohort study in which quality of life was monitored by specialist nurses using an instrument based on the EORTC QLQ-LC13. For the reasons given above, side effects diminished during the progress of the trial while we were surprised by the positive effects of MIC on tumour related symptoms. An unselected cohort of 109 patients among the 359 patients with stage IIIB or IV NSCLC randomised to receive MIC or standard PC were the basis of the quality of life study.³ Twelve tumour related and chemotherapy related symptoms were assessed on a 4 point scale (0=not at all, 1=a little, 2=quite a bit, 3=very much) at 3 weekly intervals for 15 weeks. A mean quality of life score (QLS) was calculated at each time point and a significantly greater tendency to improvement in QLS was seen over the first 6 weeks with MIC than with PC ($p=0.007$).

Over a longer time period it is important to combine quality of life data with survival data since the non-random attrition of the patients with the lowest QLS can bias quality of life studies. To achieve this the quality of life data were converted to a 0–1 “global QL score” (GQS) scale where 0=dead, 0.25=all symptoms rated as “very much”, and 1=all symptoms rated as “none”. A linear decline in GQS was assumed from the last assessment to death and the area under the curve of serial GQS was calculated to give the number of “quality adjusted life weeks” (QALW). Thus, a patient surviving 15 weeks with no symptoms of disease or toxicity would score 15 QALWs. The median QALWs for PC alone was 9.4 compared with 12 for MIC chemotherapy ($p=0.004$, Wilcoxon two sample test).

Mitomycin C, vinblastine, cisplatin (MVP)

A study of 120 patients with advanced (stage IIIB and IV) NSCLC treated with 3 weekly MVP found an objective response in 32% of patients. Relief of tumour related symptoms was achieved in 69% of patients—in 61% of responding patients after the first course and in 96% after the second course.¹¹ A formal complete or partial response was not essential for symptomatic benefit.

Gemcitabine and vinorelbine

These two agents have clinical activity in NSCLC and both are well tolerated outpatient treatments. As such, both have been evaluated as single agents in randomised trials with quality of life end points. Vinorelbine was shown to prolong life significantly and to alleviate symptoms in elderly patients (age 70+) with advanced NSCLC,¹² while gemcitabine had no effect on survival but did improve quality of life compared with supportive care alone.¹³

Taxanes

A recent multicentre phase III study compared the use of docetaxel in 204 patients with metastatic or locally advanced NSCLC, who had progressed after one or more platinum-based chemotherapy regimens, with supportive care. The initial dose

level of docetaxel (100 mg/m^2) was too toxic and was reduced to 75 mg/m^2 . Median survival was longer in the docetaxel arm, and preliminary reports of the quality of life data suggest beneficial effects compared with supportive care alone.¹⁴

"Best supportive care" (BSC)

The term "best supportive care" was first used in 1988 to describe the control arm in a trial comparing two chemotherapy regimens with no chemotherapy in advanced NSCLC.¹⁵ The phrase was adopted rapidly and has been used ever since to describe the control arm in cancer trials. However, there are problems with this term⁷:

- (1) It implies that we optimise these components of care more strenuously in trials than in routine oncology practice when there is no evidence that this is the case.
- (2) The name implies that it is effective, when usually it is not. Indeed, whenever quality of life has been reported for so-called "best supportive care" in advanced cancer it invariably declines progressively.
- (3) It suggests that we have reached the limits of progress in non-chemotherapeutic palliation (you cannot improve on the best), when clearly we have not.

This issue is not restricted to trials designed, run, and reported by oncologists evaluating chemotherapy. Bredin *et al*¹⁶ reported a randomised controlled trial of a range of nursing interventions versus BSC for breathlessness in patients with lung cancer. The change between baseline and 8 weeks was one of universal deterioration in all 11 items assessed in the BSC arm while in the intervention arm there was deterioration in seven of the 11 items and no change in four.

Attempts at palliation with RT, analgesics, corticosteroids, oxygen, antibiotics, etc remain important in advanced lung cancer alongside palliative chemotherapy and in those unsuitable for, or declining chemotherapy. Individual symptoms are alleviated in these ways. Invariably, however, where overall quality of life is monitored in the early weeks following randomisation to BSC, it deteriorates in advanced lung cancer.

Conclusions

There is now overwhelming evidence to support the use of cisplatin-based chemotherapy in advanced NSCLC. Survival benefits, although incontrovertible, are modest and, if achieved at the expense of major toxicity, hard to justify. However, an increasing body of evidence suggests that toxicity can be negligible and is more than outweighed by relief of tumour related symptoms. It also appears that patients are prepared to accept some toxicity in return for palliation. The 1990s have seen the emergence of new drugs with clear activity in NSCLC. Data are accumulating to support their use both for survival and quality of life gains.

"Best supportive care" is an unhelpful misleading term which should be avoided. In future trials it should be replaced by "standard palliative care" (SPC), with the type and frequency of key palliative interventions documented. Further research is needed to improve SPC which, at present, seems relatively ineffective in countering the inevitable subjective decline associated with an untreated advanced malignant disease.

Are there subsets of patients gaining more or less from the intervention?

The survival benefit from cisplatin based chemotherapy is modest and, in such a common disease, resource implications—if nothing else—demand the critical evaluation of patient subgroups to test the possibility that some patient categories may benefit more than others.

This question has been investigated using data from the phase III trials of MIC.¹⁷ In almost 800 cases with advanced NSCLC randomised to receive MIC chemotherapy or standard

treatment without chemotherapy the overall unstratified hazard ratio showed a 16% reduction in the risk of death with chemotherapy ($p=0.02$). This benefit was seen for both locally advanced and extensive stage disease (significantly in extensive disease). Subgroups defined by sex, age, and histology consistently benefited from chemotherapy. The hazard ratios for the three levels of performance status suggested that those with PS 2 gained no survival benefit from chemotherapy, in spite of the fact that they received a comparable number of courses of chemotherapy to patients with a better performance status.

The investigation of subgroups within the meta-analysis data² showed no difference in the effect of chemotherapy in patients with good (PS 0 and 1) and poor (PS 2, 3 and 4) performance status; although the subgroup of PS 2 patients was fairly small ($n=159$), our findings are consistent with other studies¹⁸ and therefore need confirmation. The findings from the subgroup analysis are particularly important given the recent trend to exclude PS 2 patients from major chemotherapy trials. In a South West Oncology Group (SWOG) trial,¹⁹ for example, PS 2 patients were excluded from the onset, while in an Eastern Cooperative Oncology Group (ECOG) trial unexpected excessive toxicity was observed in PS 2 patients and hence the protocol was amended during the trial to exclude them.²⁰

In contrast to this possible lack of effect on survival, PS 2 patients in the MIC trials experienced the greatest improvement in quality of life during the first 6 weeks of chemotherapy.¹⁷ Symptomatic improvement is valued highly by patients¹⁰ and this is therefore an important element when deciding on the appropriate treatment for PS 2 patients. Almost by definition, PS 2 patients will have a poorer quality of life at diagnosis and hence more scope for chemotherapeutic palliation, but also greater vulnerability to toxicity. The finding of an overall short term improvement in quality of life in the chemotherapy arm in these cases suggests that symptom palliation outweighed toxicity. It is clear that further trials are required in PS 2 cases.

What about elderly patients?

Nearly all the data on chemotherapy in NSCLC are derived from trials in which the upper age limit for entry was 75. In the UK 41% of patients are over 75.²² An Italian study¹² randomised 191 elderly patients (70 years or older) with advanced disease to receive either single agent vinorelbine or BSC. Quality of life was evaluated using the EORTC questionnaire. Vinorelbine treated patients scored better than controls on quality of life functioning scales, had fewer lung cancer related symptoms, but worse treatment related toxicity. There was a statistically significant survival advantage for patients receiving vinorelbine (two sided test, $p=0.03$) with median survival increasing from 21 to 28 weeks.

What proportion of patients with NSCLC should be considered for chemotherapy?

The use of chemotherapy in NSCLC varies widely across the UK. The National Institute for Clinical Excellence (NICE) in the UK has accepted that 5–20% of cases receive treatment depending on where they live.²¹ In order to derive an estimate of a realistic target figure, data on efficacy from the trials and meta-analyses already discussed were combined with Cancer Registry statistics on incidence and age distribution²² together with an estimate of performance status distribution within the NSCLC population of England and Wales. The latter was supported by data from the Yorkshire lung cancer referrals pattern audit of 1999 which indicated the proportion of patients having a diagnostic bronchoscopy,²³ and from the Royal College of Physicians lung cancer bronchoscopy audit of 1680 patients in 1999 in which PS was prospectively recorded.²⁴ Incorporating the cases recurring after surgery and

hence becoming eligible for consideration of chemotherapy, it was found that about 50% of all patients with NSCLC should be considered for chemotherapy during at least one stage in the natural history of their disease.²⁵

CHEMOTHERAPY IN PATIENTS WITH OPERABLE AND POTENTIALLY OPERABLE DISEASE

Preoperative chemotherapy

NSCLC is clearly responsive to chemotherapy and it seems the chance and degree of response are greater with earlier stage cases. There are a number of reports of complete pathological response in patients having preoperative cisplatin based chemotherapy. There is therefore great interest in the role of chemotherapy in early stage disease, with the intention of perhaps facilitating surgery and abolishing micrometastases.

Two randomised trials were published in 1994 which indicated a major benefit from preoperative chemotherapy in stages I–IIIA NSCLC compared with surgery alone.^{26, 27} Both of these were very small and potentially confounded, hence most collaborative groups feel that further data are necessary. In the UK the MRC LU22 trial randomises patients to receive surgery alone compared with surgery following three cycles of MIC, MVP or NP (vinorelbine plus cisplatin). In the USA the SWOG-9900 trial has a similar design but uses paclitaxel plus carboplatin. The results of these are awaited with interest.

Postoperative chemotherapy

As with preoperative chemotherapy, definitive answers to the question of the effect of adjuvant chemotherapy in operable NSCLC are awaited. The Adjuvant Lung Project in Italy (ALPI) has recently closed a trial with over 1500 cases of resected stage I–IIIA NSCLC randomised between MVP (three cycles) or no chemotherapy. The International Adjuvant Lung Trial (IALT) is of similar design but uses cisplatin plus either vinblastine, vinorelbine, vindesine or etoposide. An accrual of 3300 patients is expected by 2003. There are two other adjuvant chemotherapy trials in Europe—ANITA1 (cisplatin plus vinorelbine) and ANITA2 (vinorelbine alone)—and an intergroup American trial (cisplatin plus weekly vinorelbine for 16 weeks). If not individually conclusive, a meta-analysis of these trials should settle the question.

THIRD GENERATION AGENTS

In the 1990s an unprecedented number of new drugs, and with them new interest, emerged in the chemotherapy of NSCLC. In 2001 four of these agents (paclitaxel, docetaxel, gemcitabine and vinorelbine) were approved by NICE for use in England and Wales.²¹ Despite many trials, it has proved difficult to show conclusively that the third generation agents are more effective than the best of the earlier drugs. The superiority of cisplatin plus paclitaxel over second generation agents was based on trials in which the comparator arms were cisplatin plus either etoposide²⁸ or teniposide.²⁹ In the first case response rate and survival were better, but in the latter only response rate. Many workers in the field believe the epipodophyllotoxins to be less effective than the best five second generation agents listed above. More recent trials comparing regimens from the 1980s (such as MIC) with those from the 1990s have failed to prove superiority.^{30, 31}

Trials which compared various combinations of cisplatin with third generation agents have also been somewhat disappointing. For instance, a major ECOG trial with 5592 cases failed to demonstrate important differences between paclitaxel/cisplatin, paclitaxel/carboplatin, gemcitabine/cisplatin, and docetaxel/cisplatin.³² More importantly, response rates were low (15.3% for paclitaxel/carboplatin) and median survival rates were in the range of 7.4–8.3 months. This regimen had become the community standard in the US based on a phase II study which had reported a response rate of 60% and a median survival of more than 12 months.³³ This

was especially disappointing given the inclusion of only patients with the best performance status (PS 0, 1). Patients with PS 0, 1 had an objective response rate of 37% and a median survival of 8.3 months in the MIC2 trial (Cullen and Billingham, unpublished data).

The performance of the paclitaxel/carboplatin combination in the SWOG trial¹⁹ was similar with a response rate of 25% and median survival of 8 months. The comparator arm (cisplatin/vinorelbine) was essentially the same but with different patterns, albeit similar levels of toxicity.

Second line chemotherapy in NSCLC

Of the new agents (taxanes, gemcitabine, vinorelbine), the taxanes have been most extensively studied as second line chemotherapy. The highest response rates (7–27%) were obtained with single agent docetaxel. In a phase II study of 42 patients Fosella *et al*³⁴ reported an objective response rate of 21% in platinum refractory NSCLC, with a median survival of 42 weeks. This apparent (at least partial) lack of clinical cross resistance fits with the suggestion that taxanes can initiate apoptosis through pathways other than the p53 dependent system that is commonly mutated in cisplatin resistant lung cancers. Docetaxel is the only agent that has been reported in phase III trials of second line chemotherapy in NSCLC. Shepherd *et al*¹⁴ compared docetaxel with BSC in 196 patients with NSCLC previously treated with cisplatin-based regimens. The docetaxel dose was reduced from 100 mg/m² to 75 mg/m² following excessive toxicity, but there was an overall significant prolongation of survival and, at the lower dose, the benefits outweighed the risks. A second phase III trial compared two doses of docetaxel with ifosfamide or vinorelbine, again in patients previously treated with cisplatin based agents.³⁵ Significant differences favouring docetaxel in response rate, time to progression, and 1 year survival were observed. Combining docetaxel with other agents in the second line setting so far seems not to result in added benefit, although experience is limited.

Second line trials with paclitaxel are less consistent than with docetaxel, with response rates ranging from 0% to 38% and no phase III data. Similarly, the results with gemcitabine and vinorelbine, either as single agents or together, are conflicting, but with little cause for great optimism as second line treatment.

It is difficult to estimate the proportion of patients with advanced NSCLC who will become eligible for second line chemotherapy, but clearly it is a minority. We already suspect that the survival benefit (but probably not the palliative benefit) from first line chemotherapy is confined to those with PS 0 and 1.¹⁷ The same seems to apply with second line chemotherapy,³⁵ and the proportion of these will be smaller as disease progression has taken its toll in terms of performance status. Furthermore, the “trade off” between palliation and toxicity will be much more finely balanced during the later stages of the disease and for many patients simple non-chemotherapeutic palliation will be the best available option, accepting that it is likely to be associated with an inexorable decline in quality of life.

FOURTH GENERATION AGENTS: THE NEXT BEGINNING

Several epithelial tumours, including NSCLC, overexpress epidermal growth factor receptor (EGFR) and overproduce EGFR ligands. This permits the activation of endogenous tumour EGFR via autocrine mechanisms, resulting in processes important to cancer development and progression including cell proliferation, apoptosis, angiogenesis, and metastatic spread. Blocking of EGFR binding to ligands could thus prevent activation of receptor function and inhibit proliferation of tumour cells. A similar effect would be anticipated by

inhibiting tyrosine kinase phosphorylation of the erbB receptors, a critical early process in the intracellular transmission of the proliferative signals. EGFR is overexpressed in 40–80% and erbB2 in 30–35% of non-small cell lung cancers.³⁶

A number of different approaches are currently being used to target the EGFR. The most promising strategies in clinical development include monoclonal antibodies to prevent ligand binding and small molecule inhibitors of the tyrosine kinase enzymatic activity to inhibit autophosphorylation and downstream intracellular signalling. OSI-774 and ZD1839 (Iressa) are currently in phase II and III development, respectively. ZD1839, an orally active selective quinazoline derivative, has shown promising in vitro and in vivo antitumour activity. Preliminary results from phase I and II trials in patients with advanced disease indicate that ZD1839 and OSI-774 have an acceptable tolerability profile and promising clinical efficacy in patients with a variety of tumour types.^{37,38} The results of randomised trials of ZD1839 in advanced NSCLC are expected in 2002, and the effect of combining this agent with conventional chemotherapy is also under investigation.

If progress with chemotherapy culminating in the third generation agents represents “the end of the beginning”, then it is reasonable to consider the next generation optimistically as the beginning of the next phase. For here we have, for the first time, the emergence of drugs designed to inhibit specific biological pathways that appear crucial to tumour growth.

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